REMARKS

Reconsideration and withdrawal of the rejections of the claims, in view of the remarks herein, is respectfully requested. Claims 153-154 and 169 are amended, and claim 156 is canceled. Claims 153-155 and 157-173 are now pending in this application.

The Obviousness-Type Double Patenting Rejections

Claims 153-173 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 173-194, 196-203, 205-211 and 231 of copending U.S. patent application Serial No. 09/754,775. Applicant notes that the '775 application has not yet issued and is pending. Therefore, a terminal disclaimer is not required until issuance of that application or the present application. If a terminal disclaimer is required, it can be requested by the Office as a condition of allowance.

Claims 153-173 were also rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of U.S. Patent Nos. 5,472,985, 5,770,609, 5,595,722, 5,559,884, 5,773,479, 5,847,007, 6,074,659, 6,166,090, 6,197,789, 6,262,079 and 6,251,920. A terminal disclaimer over U.S. Patent Nos. 5,472,985, 5,770,609, 5,599,844, 5,773,479, 5,847,007, 6,166,090, 6,197,789, 6,212,079, and 6,251,920 is enclosed herewith.

The claims in U.S. Patent No. 5,595,722 are directed to a method for identifying an agent which increases the level of TGF-beta in a human, which includes contacting cultured explant human aortic smooth muscle cells (hVSMC) with the agent in an amount effective to reduce or inhibit the rate of proliferation of the cells; contacting the hVSMC resulting from step with a moiety which specifically binds to TGF-beta in an amount effective to block the binding of TGF-beta to the TGF-beta receptors of the hVSMC and determining the rate of proliferation; and determining whether the rate of proliferation is increased relative to the rate of proliferation of the hVSMC which are contacted with the agent.

The claims in U.S. Patent No. 6,074,659 are directed to a therapeutic method, in which procedural vascular trauma associated with placement of a device in a vessel is treated by administering to a mammal a cytostatic amount of an agent that does not exhibit substantial cytotoxicity, wherein the agent is a cytoskeletal inhibitor.

The claims in U.S. Patent No. 5,559,884 are directed to a computer system having a method for encoding a signature in a plurality of copies of a computer program. Note that U.S. Patent No. 5,559,884 is not commonly assigned relative to the present application.

In contrast, the present claims are directed to the use or identification of a cytostatic dose of an agent for TGF-beta elevation.

Therefore, withdrawal of the obviousness-type double patenting rejections is respectfully requested.

The 35 U.S.C. § 112 Rejection

Claims 153-168 were rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not reasonably provide enablement for preventing a vascular indication in a mammal. This rejection is respectfully traversed.

In this regard, the Examiner is requested to consider Example 7. Example 7 discloses that adult mice were fed a normal or high fat diet ± tamoxifen (TMX), a TGF-beta elevating agent. As shown in Table 2, TMX administration reduced the number and size of lesions in those mice. Therefore, TGF beta elevating agents like TMX can prevent vascular disorders.

Accordingly, withdrawal of the 112(1) rejection is respectfully requested.

The 35 U.S.C. § 103 Rejections

Claims 153-155 and 157-173 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Grainger et al. (Biochem J., 294:109 (1993)) in view of Nuovo et al. (Int. J. Gyn. Path., 125 (1989)) and further in view of Purchio et al. (U.S. Patent No. 5,221,620). Claims 153-155 and 157-173 were also rejected under 35 U.S.C. § 103(a) as being unpatentable over Grainger et al. in view of Bjorkerud (Arterioscler. Thrombosis, 11:892 (1991)) and further in view of Purchio et al. Claims 153-155 and 169 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Fischer et al. (Exp. Mol. Pathology, 43:288 (1985)) in view of Grainger et al. and further in view of Purchio et al. Claims 153-159, 164-165 and 168 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Sawada et al. (Pharmacometrics, 1992) in view of Ellis et al. (U.S. Patent No. 4,826,876). Claims 153-155, 157-159, 164-165, and 168 were

rejected under 35 U.S.C. § 103(a) as being unpatentable over Gylling et al. (Atherosclerosis, 96:245 (1992)) in view of Ellis et al. These rejections are respectfully traversed.

To establish a *prima facie* case of obviousness, the Examiner must meet three criteria. The Examiner must establish that (1) there is some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings; (2) there is a reasonable expectation of success; and (3) the prior art reference (or references when combined) teach or suggest all the claim limitations. See M.P.E.P. § 2143. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

Grainger et al. disclose that abnormal proliferation of vascular smooth muscle cells (VSMCs) is a major component of vascular disease, including atherosclerosis, vascular rejection and restenosis following angioplasty, and that agents which selectively inhibit VSMC proliferation may prevent or inhibit the progress of those diseases (page 109). Grainger et al. relate that TMX decreases the rate of proliferation of rat aortic VSMCs *in vitro* by inducing the production of transforming growth factor-beta (TGF-beta; Abstract, and bridging paragraph at pages 110-111). Grainger et al. also relate that TMX stimulates the production of latent TGF-beta and promotes the activation of latent TGF-beta (page 111). Based on these observations, Grainger et al. speculate that TMX may be useful to elevate TGF-beta in patients undergoing therapeutic angioplasty.

Nuovo et al. teach that TMX treatment is associated with endometrial polyp proliferation and thick-walled blood vessels (pages 126 and 128), which provides a teaching away of using agents such as TMX and analogs thereof in indications including vascular indications characterized by a decreased lumen diameter.

Purchio et al. disclose the cloning of TGF-beta2 nucleic acid from RNA isolated from PC3 (prostate adenocarcinoma) cells treated with TMX.

Bjorkerud discloses the *in vitro* effect of TGF-beta1 on SMCs, i.e., the promotion of myodifferentiation and inhibition of SMC growth.

Fischer et al. treated female rabbits on an atherogenic diet with cottonseed oil, TMX, testosterone or progesterone (abstract). It is disclosed that TMX treatment was associated with increased collagen and elastin accumulation (abstract and page 294). The authors conclude that based on indirect evidence, TMX treatment decreases degradation, thereby resulting in a tendency to increase accumulation (page 294). Nevertheless, the authors point out that the apparent decreased synthesis of connective tissue seen in TMX-treated animals is somewhat obfuscated by the fact that the rabbits were not eating well toward the end of the experimental period (page 294). The authors concede that the results for TMX in the study are open to several interpretations and that further study is indicated to clarify the mechanisms of effect of TMX on arterial connective tissue.

Gylling et al. studied cholesterol synthesis in a woman with breast cancer before and during TMX treatment. The authors of Gylling et al. conclude that TMX inhibits cholesterol synthesis, resulting in an increase in the cholesterol precursor Δ^8-cholesterol, which has harmful side effects (page 246).

The Examiner acknowledges that the references do not specifically teach determining an agent for TGF-beta elevation or selecting a cytostatic dose of the agent (pages 8, 10 and overlapping sentence on pages 11-12 of the Office Action) or that smooth muscle cell proliferation is associated with procedural vascular trauma (pages 8 and 10 of the Office Action). However, the Examiner asserts it would have been obvious to one of ordinary skill in the art at the time of the invention to treat a vascular indication by the administration of an agent that elevates TGF-β levels, and that the motivation to do so is provided by Grainger et al. or Fisher et al. (pages 8 and 11 of the Office Action). The Examiner continues asserting that the dosage or selection of an agent or mode of administration is a parameter that a person of ordinary skill in the art would routinely optimize and that one of ordinary skill in the art would have been motivated to administer an agent that decreases the proliferation of SMC in general to any condition related to SMC proliferation in order to achieve similar therapeutic benefits (pages 8, 10 and 12 of the Office Action).

With respect to the rejection of the claims under § 103 over Grainger et al., Nuovo et al. and Purchio et al., none of Grainger et al., Nuovo et al. or Purchio et al., alone or in combination, disclose or suggest the use or identification of a cytostatic dose of an agent for TGF-beta

elevation that has reduced estrogenic activity or DNA adduct formation relative to TMX. In particular, there would be no motivation to administer agents that elevate TGF-beta levels such as TMX and analogs thereof as Nuovo et al. teach away from the use of TMX and analogs thereof.

With respect to the rejection of the claims under § 103 over Grainger et al., Bjorkerud, and Purchio et al., Bjorkerud do not supplement what is missing in Grainger et al. and Purchio et al., as Bjorkerud discloses the *in vitro* effect of TGF-beta1 on SMCs, i.e., the promotion of myodifferentiation and inhibition of SMC growth. Therefore, the combination of Grainger et al., Bjorkerud and Purchio et al. does not teach or suggest the use or identification of a cytostatic dose of an agent for TGF-beta elevation that has reduced estrogenic activity or DNA adduct formation relative to TMX.

Moreover, the combination of Fisher et al., Gylling et al. and Purchio et al. does not teach or suggest the use or identification of a cytostatic close of an agent for TGF-beta elevation that has reduced estrogenic activity or DNA adduct formation relative to tamoxifen. Further, Gylling et al. teach away from the use of TMX and analogs thereof, as TMX administration is disclosed in Gylling et al. to result in an increase in a cholesterol precursor with harmful side effects.

Sawada et al. disclose that in order to evaluate the safety of toremifene, which is expected to be used in the treatment of breast cancer, toremifene was administered to female rats (page 1 of the translation). It is disclosed that the animals were divided into a control group and groups administered 0.01, 0.1, 1 and 10 mg/kg toremifene per day. These amounts were based on earlier studies where a 0.7 mg/ml group showed toxic changes, including suppressed weight gain and total cholesterol reduction. Sawada et al. teach that the decrease in cholesterol is part of a general toxic syndrome arising from higher than appropriate dosages of toremifene, which corresponds with suppressed weight gain and a drop in feed consumption. Sawada et al. also link decreased cholesterol to a change in liver function, which, in the case of tamoxifen, can be associated with liver tumor formation. See Sawada et al. at page 13. Sawada et al. teach against the use of such dosages, due to the associated toxicity. Based upon the disclosure of Sawada et al., it is unclear whether the reduction in total cholesterol is due to the action of toremifene on TGF-beta levels, whether it is due to the toxicity of toremifene, or if it is due to the decrease in feed consumption.

Ellis et al. relate to chemical compounds such as 3,5-dibromo-3′-[6-oxo-3(1H)-pyridazinyl-methyl]-thyronine that have selective thyromimetic activity (abstract). Ellis et al. disclose that antihyperlipidaemic agents that lower the LDL-cholesterol to HDL-cholesterol ratio are indicated as antiatherosclerotic agents.

Ellis et al. do not supplement what is missing in Sawada et al. or Gylling et al., because none of Sawada et al., Gylling et al. nor Ellis et al. discloses or suggests the use or identification of a cytostatic close of an agent for TGF-beta elevation that has reduced estrogenic activity or DNA adduct formation relative to tamoxifen. Further, both Sawada et al. and Gylling et al. teach away from the use of TMX or analogs thereof, as toremifene administration was found to result in a general toxic syndrome and TMX administration was found to result in an increase in a cholesterol precursor with harmful side effects, respectively.

Applicant respectfully submits that the Examiner has not established the *prima facie* obviousness of the present claims in view of any combination of the cited documents. Thus, withdrawal of the § 103 rejections is respectfully requested.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Mail Stop Amendment, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 1st day of October, 2007.

Dawn M Poole _____ Dawn M Poole

Name Signature